REMARKS

A. Rejection of Claims 37 Pursuant to 35 U.S.C. 112, Second Paragraph

Claims 37 stands rejected pursuant to 35 U.S.C. 112, second paragraph as failing to distinctly point out and claim the subject matter of the invention. The Office Action states:

> Claim 37 provides fo a diagnostic kit of parts containing a selectively replicating virus and a transgene expression cassette containing a reporter gene with appropriate instructions for use, but sinc eht claim does not set forth any steps in the method/process, it is unclear what method applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active positive steps delimiting how this actually practiced.

Applicants traverse.

Applicants wish to point out that the claims are not directed to a process, but rather to a composition of matter, i.e. a kit containing a selectively replicating vector wherein the vector expresses a marker transgene. The claims are read in light of the specification. The specification provides numerous examples of selectively replicating vectors expressing marker transgenes. Data demonstrating the selective expression of marker genes in pathway deficient cells is provided in Tables 2-6. Details of the construction of these vectors is provided in the Examples. Additionally, the diagnostic applications of such vectors are described at pages 34-35 of the specification. From a review of the specification, one of skill in the art would readily appreciate the uses of the diagnostic kit described. While the specification must teach one of skill how to make and use the invention, it is not necessary that claims directed to a composition of matter also contain a limitations to their method of use. Applicants therefore believe that the rejection set forth by the Examiner pursuant to 35 U.S.C. 112 second paragraph is improper and respectfully request that this ground of rejection be withdrawn.

B. Rejection of Claim 37 Pursuant to 35 U.S.C. 101:

Claim 37 stands rejected pursuant to 35 U.S.C. 101 because "the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper defintion of a process, i.e. results in a claim which is not a proper process claim under 35 U.S.C. 101." Applicants traverse.

As stated above, the Applicants wish to note that the claim is directed to a composition of matter not a process. Consequently applicants believe that the rejection pursuant to 35 U.S.C. 101 is not well founded and is improper. Applicants therefore respectfully request that this ground of rejection be withdrawn.

C. Status of Claims 1-13 and 38-40:

Applicants are confused by the claim rejections indicated on the Office Action Summary in view of the comments made in the body of the Office Action. The Office Action Summary indicates that Claims 1-40 are rejected. However, a review of the text of the Office Action has no comments regarding, or setting forth any ground of rejection relating to, claims 1-13 and 38-40. Indeed the only mention of specific claims subject to rejection relates to claims 14-36 (*see* Office Action at page 3, first paragraph). From Applicants' review of the Office Action, Applicants believe that the Examiner has only set forth rejections of the claims directed to pharmaceutical formulations (claims 14-28), method of use claims (claims 29-33), the claim to a cell transformed with a selectively replicating viral vector of the invention (claim 34) and the claims directed to pathway responsive promoters (claims 35 and 36). The balance of the comments in the Office Action address only 14-36. In the absence of a specific rejection of the claim, Applicants believe they are entitled to assume that the subject matter of claims 1-13 and 38-40 is allowable.

Furthermore, the Examiner's comments regarding the subject matter of claims 1-13 (directed to selectively replicating viral vectors) and claims 38-40 (directed to methods of producing the vectors in producer cell lines) support this conclusion. The Examiner states at page 3 of the Office Action:

> the specification ***while enabling for an in vitro method of utilizing a selectively [replicating] adenoviral vector*** comprising a pathway responsive promoter such as p53, TGF-beta or RB promoter linked to a repressor of viral replication such as E2F-Rb and the specification ***while being enabling for a method of making a selectively replicating viral vector*** by infecting producer cells such as 293 cells and A549 cells...(***emphasis added***)

In order to provide an enabling disclosure for a composition of matter, the specification need only set forth a ***single*** utility for the claimed subject matter. There is no requirement that all potential uses of a composition of matter be described in order to satisfy the enablement requirement. Consequently, although with acceding to the Examiner's position regarding an alleged lack of *in vivo* utility, Applicants believe that the utility requirement for the claimed subject matter of claims 1-13 and 38-40 has been met by the Applicants and acknowledged by the Examiner's own statements regarding *in vitro* utility.

Applicants therefore believe that the indicated rejection of Claims 1-40 on the Office Action Summary is in error and that only claims 14-36 are rejected and that claims 1-13 and 38-40 are allowable. Applicants wish to receive confirmation of the allowability of these claims in future correspondence.

D. Rejection of Claims 14-36 Pursuant to 35 U.S.C. 112, First Paragraph

Claims 14-36 stand rejected pursuant to 35 U.S.C. 112, first paragraph as stated by the Examiner:

> Claims 14-36 are rejected under 35 U.S.C. 112 first paragraph, because the specification while enabling for an *in vitro* method of utilizing a selectively [replicating] adenoviral vector comprising a pathway responsive promoter such as p53, TGF-beta or RB promoter linked to a repressor of viral replication such as E2F-Rb and the specification while being enabling for a method of making a selectively replicating viral vector by infecting producer cells such as 293 cells and A549 cells, fails to provide enablement for the *in vivo* method of treating any cancer by a pharmaceutical formulation administered to a subject; or a method of killing a cell with a pathway defect by contacting the target cell with a selectively replicating recombinant adenovirus comprising a pathway responsive promoter operably linked to a repressor of viral replication, to eliminate tumor cells from stem cells. The specification does not enable any person skilled in the art to which it pertains, or to which it is most nearly connected, to make and or use the invention in scope with these claims.

The Applicants traverse. There are four groups of claimed subject matter within the scope of claims 14-36 currently subject to rejection:

(1) pharmaceutical formulations (claims 14-28),

(2) method of use claims (claims 29-33),

(3) the claim to a cell transformed with a selectively replicating viral vector of the invention (claim 34), and

(4) the claims directed to pathway responsive promoters (claims 35 and 36).

The Applicants will address the Examiner's positions in turn with regard to each of these individual subject matters.

(1) Pharmaceutical Formulation Claims 14-28:

Claims 14-28 are directed to pharmaceutical formulations of selectively replicating viral vectors comprising a pathway responsive promoter driving a repressor of viral replication. The Examiner states that the specification fails to provide one of skill in the art in the preparation of the pharmaceutical formulations of the claimed vectors stating:

> The specification teaches only generally, the routes of administration of the pharmaceutical formulation and delineates the possible carriers which could be used with the formulation to enhance stability, sterility, and deliverability of the therapeutic compound. (Office Action at Page 5).

Applicants traverse.

In order to satisfy the enablement requirement for claims directed to pharmaceutical formulations, it is necessary only that the skilled artisan would be able to prepare functional formulations based either on the teaching of the specification or by relying on that which is known in the literature. The specification need not teach, and preferably does not teach, that which is known in the art. The formulation of viruses for clinical use is well documented in the scientific literature. For example, a wide variety of attenuated viruses are commonly used as vaccines and the formulation of such viruses is well known. There is no reason to suspect that the formulation of the present vectors would be unusual since the replicating viruses of the present invention contain modifications primarily at the DNA level (other than the viruses containing surface targeting modifications to viral coat components) and do not affect viral coat components. It would be unduly burdensome and superfluous for the Applicants to recite the variety of formulations used for more than 40 years in the field of vaccines as examples of acceptable formulations of viruses for clinical use. Additionally, there are numerous reports of clinical trials in human beings available in the scientific literature which provide examples of clinically acceptable formulations of recombinant viral vectors. The clinical experience with recombinant vectors, such as recombinant adenoviral vectors, has demonstrated that quite simple formulations such as phosphate buffered saline commonly employed in the laboratory are suitable vehicles for such vectors. Applicants believe that the extensive clinical and manufacturing experience in the formulation of viruses for clinical applications could readily be applied by those of skill in the art to produce clinically acceptable formulations of the viral vectors of the present invention.

Additionally, contrary to the Examiner's assertions, the Applicants do believe that the specification provides extensive teachings in addition to those already available to those of skill in the art sufficient to guide the artisan in the preparation of the preferred formulations of the vectors of the present invention. Pages 27-30 of the specification provide detailed guidance in the preparation of pharmaceutically acceptable formulations of the vectors of the present invention. As indicated, certain agents may optionally be added to conventional viral formulations to enhance viral uptake. For example, the use of ethanol to enhance gene transfer is described in Engler, *et al.* United States Patent No. 5,789,244 entitled "Compositions and methods for the treatment of cancer using recombinant viral vector delivery systems" filed on January 8, 1996. The specification teaches that detergents and surfactants may optionally be included in the formulations to enhance gene transfer. Numerous specific examples of such agents which enhance gene transfer are specifically indicated in the specification. Consequently, the teaching of the specification supplants the knowledge already available to the skilled artisan in the preparation of particularly preferred formulations of the claimed vectors.

Consequently, Applicants believe that the Examiner's unsupported assertion that one of skill in the art would not have sufficient guidance based on the specification and that which is known in the art to formulate the vectors of the present invention for clinical application is not supported by (and indeed is contradicted by) the facts. Applicants therefore believe that the

Examiner's rejection of claims 14-28 directed to pharmaceutical formulations of the vectors of the present invention pursuant to 35 U.S.C. 112 is improper and respectfully request that this ground of rejection be withdrawn.

(2) Method of Use Claims 29-33:

Claims 29-33 are directed to methods of use of the vectors of the present invention. Claims 29-33 relate to relate to a method of killing a cell with a pathway defect by contacting the cell with a selectively replicating vector of the present invention. As previously discussed, the Examiner has indicated that the vectors of the present invention have been demonstrated to have *in vitro* utility in achieving selective replication in cells containing pathway defects. However, the Examiner states that the scope of the claims contemplate both *in vitro* and *in vivo* utilities and asserts that the Applicants have not enabled one of skill in the art to use the vectors of the present invention *in vivo*. In particular, the Examiner indicates that the specification fails to provide the skilled artisan with sufficient guidance to make and use the vectors of the present invention for the treatment of disease states *in vivo* without undue experimentation because:

(a) that the specification fails to provide sufficient guidance regarding dosage regimens to enable one of skill in the art to use the vectors of the present invention to achieve a therapeutic effect;

(b) that the specification fails to teach how one of skill in the art would identify target cells which could subject to be administration of selectively recombinant viral therapy;

(c) that the specification fails to enable one of skill in the art to construct recombinant adenoviral vectors having particular deletions in the E1 region;

(d) that the specification lacks teaching in regard to the combination of the vectors of the present invention in combination with chemotherapeutic agents to achieve therapeutic effect;

(e) that while the specification provides examples of certain pathway responsive promoter elements, the specification fails to provide sufficient guidance in the construction of pathway responsive promoters to facilitate the selective expression of the expression of the repressor of viral replication encompassed by the scope of the claims;

(f) that the specification fails to provide sufficient guidance in the use of immunosuppressive agents to mitigate the immune response to the recombinant vectors *in vivo*;

(g) that the specification fails to provide sufficient guidance regarding the *ex vivo* method of purging cancer cells from stem cell products because insufficient guidance is provide regarding the quantity of vector necessary to achieve the desired level of purging;

(h) that the specification fails to provide an enabling disclosure for the use of PCR to amplify the desired nucleic acid (primer) sequence by failing to give the experimental conditions under which this PCR would have taken place, how the primers were selected and manufactured and under what experimental conditions digestion and ligation of the PCR product occurred; and

(i) that although the use of vectors encoding p53 to treat cancer is well established, the use of selectively replicating vectors such as those of the present invention have not been employed in the treatment of cancer in human beings and the results of such use would be unpredictable.

Applicants traverse this ground of rejection by addressing the reasons set forth by the Examiner as summarized above in turn.

(a) Dosing Regimens:

The Examiner states that:

> The specification fails to provide an enabling disclosure as no teachings are present in terms of effective dosage of selective recombinant adenoviral vector particles to be used in the pharmaceutically acceptable formulation of the instant invention. No mention is made of how many selective recombinant adenoviral particles would be needed per target cell type, or whether this dosage would fluctuate depending upon the pathway responsive promoter used, or whether specific tumor cell types would require higher multiplicity of infections, and whether increasing selective recombinant adenoviral particle production would be more or less labor intensive as outlined in the specification. (Office Action at page 6).

Regarding the specifics of dosage, the selection of specific dosage regimens to employ the vectors of the present invention, Applicants again believe that such expertise is within the skill of the clinicians in this field. As recognized by the courts, the skilled artisan in the field of biotechnology possesses a very high level of training. The individuals who would generally be employing the vectors of the present invention are particularly cognizant of the scientific literature in the field. Indeed there are a number of "physician sponsored INDs" for clinical trials of recombinant viral vectors approved by the FDA and receiving NIH funding further attesting to the fact that clinicians in this field are of a particularly high caliber.

Additionally, there is a significant body of scientific literature in this field which would readily guide the clinician in employing these agents. For example, Applicants would note that the standard of care in the treatment of cancer is to administer the maximum tolerated dose (MTD). It is well documented in the scientific literature that replication deficient adenoviruses encoding the p53 tumor suppressor gene have been administered to human beings in ovarian cancer clinical trials in dosages of greater than 10^{13} viral particles per dose. This dose has been administered and is well tolerated throughout a three week dosage regimen of 5 daily doses resulting in the administration of more than 10^{14} viral particles over a period of three weeks.

This work is presented in the Nielsen, *et al.* reference provided on page 32 and is also contained in published scientific articles which can be supplied. Additionally, wild-type and attenuated viruses have been administered to human beings in additional clinical trials and clinical experients. Early reports in the literature demonstrate the use of wild-type vectors for therapeutic use. Although these studies are not well characterized by modern standards, they do demonstrate the ability to use replication competent, indeed fully wild-type, vectors *in vivo*. More recent clinical experiments conducted by Onyx Pharmaceuticals, Inc. with the ONYX-015 virus (a recombinant adenovirus containing a deletion in the E1b55K region as described in United States Patent 5,677,178 cited on page 1 of the specification) are currently under clinical investigation in human clinical trials for the treatment of head and neck cancer. The clinical protocols and results of these studies have been published in the scientific literature and presented at numerous scientific conferences. These scientific studies in human beings provide a great deal of guidance to the skilled artisan in the specifics of route of administration and dosage regimens which are acceptable in the human being.

Finally, the examiner questions whether one of skill in the art would be able to determine whether certain tumor cell types would require greater multiplicities of infection to sustain clinical effect. First, there is nothing to indicate that certain tumor types would require significant adjustments to the dosage. As previously discussed, the typical practice in the field of oncology is to dose at the maximum tolerated dose which has been established in numerous clinical studies. The specification also provides examples of the ability to infect and replicate in a broad range of tumor cell types at a representative particle concentration. Table 5 provides data from 15 different tumor cell lines derived from a variety of tissue cell types demonstrating the ability of the viruses to replicate efficiently in a variety of tumor cell types containing defects in the p53 pathway. Similarly, Table 2 provides examples of the ability of the vectors of the present invention to selectively infect and replicate selectively in six different tumor cell lines containing TGF-beta pathway defects.

Consequently, Applicants believe that they have provided substantial evidence that the dosing regimens to be employed with the vectors of the present invention are well established in the scientific literature and known to those of skill in the art to which the invention pertains. Applicants therefore believe that the examiner's concerns in this regard have been addressed and respectfully suggest this basis of rejection has been traversed.

(b) Identification of Appropriate Target Cells:

The Examiner asserts that the specification is not enabling for *in vivo* application because it fails to specifically identify target cells which could be treated by administration of selectively recombinant viral therapy.

> Applicant teaches that by the use of various pathway responsive promoter elements, one can target the expression of the virus to any given cell with an intact pathway pg.10. Applicant does not provide guidance of how one would determine whether or not a cell

> has an intact pathway or how one would determine the type of mutation present in a specific target cell, or how one would determine in a particular instance, which pathway responsive promoter would be best suited to encode the viral replication repressor to target a specific cell, and finally how one would determine in vivo efficacy of the combined therapy.

Applicants disagree and traverse.

First, the ability to use the vectors *in vivo* does not necessarily require that the clinician identify the pathway status of the tumor cells to be treated. The vectors have been demonstrated to selectively replicate in tumor cells containing pathway defects. It is well known in the scientific literature that approximately 60% of tumor types identified to date contain defects in the p53 gene. When considering p53 pathway defects in addtion to p53 mutations, this percentage is higher. Additionally, a significant number of tumors types have been identified as containing TGF-beta or Rb pathway defects. There is no requirement that the vectors of the present invention be functional in all tumor cell types, only that they are effective in some tumor types. Based on the data presented, it is clear that the vectors of the present invention are able to selectively replicate in cells having p53, Rb and TGF-beta pathway defects representative of the majority of human tumors identified to date. Additionally, even though it is not necessary for its *in vivo* application of the claimed vectors, it is not difficult for the skilled artisan to determine the p53, TGF-beta, or Rb status of cells obtained from a tumor biopsy sample using conventional techniques.

(c) Construction of Adenoviral Vectors Containing E1 Deletions:

The Examiner suggests that the specification fails to provide sufficient guidance to construct recombinant adenoviral vectors containing specific deletions in the E1 region exemplified by the subject matter of claims 12-13 stating:

> The specification fails to provide an enabling disclosure because no mention is made of one would have constructed the selective recombinant adenoviral vector with the deletion in the E1a region. Neither is information given in terms of the plasmids used to construct the vector, how the recombinants would have been purified and titred before use.

Applicants disagree and traverse.

First, this rejection appears to relate to the compounds of claim 12-13 and not to the formulation or method claims subject to rejection. Thus the Applicants do not believe that this rejection is properly addressed to the method of use and formulation claims at issue. Applicants have already discussed this point in detail above.

However, in order to address the Examiner's concerns on this point, the Applicants would offer the following comments. The E1 region of recombinant adenoviruses has been extensively investigated and characterized. See, e.g. Mulligan (1990) Science 260:926-932; Jones and Shenk, 1979, PNAS(USA) 76(8):3665-3669; Horwitz, M. in Virology, B.N. Fields Ed.

(Raven, New York, 1990) Chapter 60). Whyte, *et. al.* (1989) Cell 56:67-75, described with particular clarity the regions of E1a which are responsible for Rb, p107 and p300 binding. Howe, *et. al.* (1990) PNAS 87:5883-5887 describe the particular deletions in of amino acids 4-25 and 111-123. Each of the studies reported above utilized recombinant adenoviruses containing specific deletions in the E1 region and each reference discloses the materials and methods used to construct such viruses. Furthermore, the method for the purification of adenoviral vectors is known to those of skill in the art. A process for the purification of adenoviral vectors suitable for human therapeutic applications may be achieved by Shabram, *et al.* United States Patent No. 5,837,520 entitled "Method of purification of viral vectors" filed on March 7, 1995. This patent corresponds to the then pending United States patent application mentioned at page 36 of the specification. Consequently, since generalized techniques for constructing recombinant E1 modified adenoviruses are well known in the literature and the E1 region has been extensively characterized, Applicant believes that one of skill in the art would know how to construct recombinant adenoviral vectors containing specific deletions in the E1a region as claimed.

(d) Combination Chemotherapy Treatment Regimens:

The Examiner suggests that the skilled artisan would not possess sufficient guidance based on the teaching of the specification and that known to those of skill in the art to administer the vectors the present invention in combination with conventional chemotherapy agents. The standard of care in the oncology field is to administer agents in combination therapy protocols. Modern clinical trials involving replication competent and replication deficient recombinant adenoviruses are conducted in combination with chemotherapeutic agents. Recombinant adenoviral vectors encoding p53 have been administered in combination with a variety of chemotherapeutic agents such as cisplatin, carboplatin, and taxol without unusual adverse results. As previously discussed, these treatment regimens have been described in the literature. It is well known in the art that the standard of care for the use of anti-cancer agents (whether small molecules or biologics) is to administer such agents in conjunction with other chemotherapeutic agents. Examples of the combination of recombinant vectors encoding p53 and DNA damaging agents for the treatment of cancer are described in Roth, *et al.* United States Patent 5,747,469 issued May 5, 1998 and Roth, *et al.* United States Patent 6,069,134 issued May 30, 2000. Particular protocols for the administration of recombinant adenoviral vectors are described in Nielsen, *et al.* reference cited in the specification. Therefore, there is nothing to suggest that the combination of recombinant viral vectors and conventional chemotherapeutic agents would result in unexpected adverse *in vivo* results. In fact, the data is to the contrary and that such combinations provide enhanced therapeutic effects.

Applicants believe that they have provided significant evidence to counter the Examiner's suggestion that the skilled artisan would not know how to combine the vectors of the present invention in a combination therapy with other chemotherapeutic agents based on actual clinical experience. Consequently, Applicants believe that they have traversed this basis of rejection.

(e) Construction of Additional Pathway Responsive Promoters:

The Examiner states that the specification fails to provide sufficient guidance in regard to the construction of additional pathway responsive promoters beyond those specifically exemplified. As discussed in the specification, a variety of promoter regions are well known in the literature. Applicants have provided specific examples of such promoters along with scientific papers and patents describing the sequence and isolation of such pathway responsive promoter regions. See the specification at pages 8, 9, and 10. Applicants therefore disagree with the Examiner's characterization that the skilled artisan would not be able to be isolate and identify additional pathway responsive promoters.

(f) Use of Immunosuppressive Agents to Mitigate Immune Response:

The use immunosuppressive agents would be a matter well understood by clinicians for the reasons already of record. The quantity of immunosuppressive agents commonly administered to human beings to achieve immunosuppression can readily be determined by following the instructions on the package insert of such agents and well known to clinicians in the field. There is no reason to suggest that the subsequent administration of the viral vectors of the present invention would alter the pharmacokinetic or pharmacodynamic properties of immunosuppressive agents. Furthermore, the use of immunosuppressive agents has not been deemed necessary in the clinical experience with recombinant viral vector therapy. There is no reason to suggest that it would be *necessary* to use an immunosuppressive agent to effectively employ the vectors of the present invention. Consequently Applicants do not believe that the Examiner's concerns in this regard are well founded and respectfully submit that the Examiner's allegations in this regard are misplaced.

(g) *Ex vivo* Stem Cell Purging Protocols:

The Examiner states:

> The specification provides a method o ablating neoplastic cells by ex vivo transduction. However, no guidance is provide which would allow the artisan to determine how many transfectants would be needed to achieve a "3 log purge or preferably a 5-log purge." The specification fails to provide an enabling disclosure for the delivery of ex vivo transduced cells to the subject. No mention is made of how many cells would be administered and the frequency of administration. In addition, no guidance is given as to how one would have separated the stem cells from its tumor cell products and how the cells would have been reintroduced into the subject.

Applicants traverse.

Regarding the process for isolation of stem cell products, the Examiner's attention is directed to the field of conventional apheresis procedures and the practice of "stem cell rescue" regularly practiced by oncologists in the clinical setting . A variety of equipment is commercially available to the clinician for the effective isolation of stem cell products. A source of such equipment (Cobe International) is described at page 33 of the specification. These

procedures are commonly employed in radiation therapy protocols for the treatment of cancer wherein the patient's stem cells are "rescued" prior to high dose radiation therapy and re-implanted to the patient on a routine basis. Applicants can provide numerous scientific references regarding this conventional procedure if desired.

Regarding the Examiner's allegation that the specification does not provide specific guidance regarding the quantity of material necessary to produce effective purging of stem cell products, applicants disagree. At page 33, the specification states:

> In the preferred practice of the invention, a stem cell product of 100 ml volume would be treated at particle number to nucleated cell ratio of approximately 2 x 10^{11} of the vectors of the present invention for a period of approximately 4 hours at 37C.

Contrary to the assertions of the Examiner, the Applicants have specified detailed reaction conditions to achieve the preferred level of purging (i.e. a 3-log or 5-log purge) of a 100 ml stem cell product. Applicants therefore believe that the Examiner's comments on this point are in error and that the specification does provide sufficient specific guidance regarding the use of these vectors in an *ex vivo* stem cell purging protocol.

(h) Construction of PCR Reagents:

The Examiner states:

> The specification fails to provide an enabling disclosure for the use of PCR to amplify the desired nucleic acid primer sequence by failing to give the experiment conditions under which this PCR would have taken place, how the primers were selected and manufactured and under what conditions digestion and ligation of the PCR product occurred.

Applicants would draw the Examiner's attention to Examples 2 and 3 which specifically provide sequences of the individual PCR primers employed. The rationale for their construction would readily be apparent to those of skill in the art based on the published sequences of the promoters. Oligonucleotides are readily prepared using commercially available equipment. Applicants employed conventional PCR procedures ***well*** established in the literature and available from Perkin-Elmer. Conventional ligation procedures were employed and need not be repeated in the specification since they are readily available in any conventional Molecular Biology laboratory handbook. Applicants believed that the inclusion of such detail would be unnecessary as anyone skilled in the art of molecular biology would not require such specificity. Applicants can readily provide a significant volume of literature on the use of PCR technology to demonstrate this fact. Consequently, Applicants believe that the Examiner's comments on this point are not well founded.

(i) Use of Vectors Would be Unpredictable

The Examiner has indicated that the field of gene therapy is a technology which is highly unpredictable requiring particular teaching to those of skill in the art to practice the claimed

invention. The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. MPEP 2164.03 *citing In re Fisher* 166 USPQ 18, 24 (CCPA 1970). Whether or not any agent will be effective in the treatment of human beings bears a certain degree of uncertainty. However, the fact that most compounds which are proposed for clinical investigation do not result in FDA marketing approval has not been a bar to patentability. Consequently, in the case of gene therapy agents, the focus on the degree of teaching required to enable the scope of the claims more properly focuses on the level of knowledge in the art. Applicant has already discussed the high skill levels of those in the art. Applicant believes that the high levels of skill and knowledge in this art are sufficiently such that a limited disclosure would enable one of skill in the art to practice the full scope the claimed invention.

Although gene therapy is a comparatively new field of therapy, one may legitimately argue that the level of understanding supporting these clinical trials is much greater than at any time in the past. The tools available to the skilled artisan is able to generate a tremendous quantity of data in a much reduced period of time using new technologies with relative ease. The advent of genomics and proteomics technologies coupled with sophisticated assay systems enables the ordinarily skilled artisan to generate a tremendous amount of data regarding the potential activity of a compound in a very short period of time. The "chip" or "microarray" technology to evaluate the response of genes in multiple cell types in response to a stimulus did not exist 10 years ago. However, a scientist may now rapidly evaluate the response of many thousands of genes in a cell in response to a potential pharmaceutical. This technology is available to the scientific community from companies such as Incyte Therapeutics (Palo Alto, CA) and Millenium Pharmaceuticals (Boston MA). Using these new technologies, agents that are proposed for clinical investigation at the present time have significantly more data to support their utility than at any time in the past. Compounds that were brought to the clinic in the 1970's had comparatively little background information regarding mechanism of action. The mere fact that gene therapy is a relatively new technology in terms of years does not mean that it is not supported by a wealth of scientific data.

As discussed in the MPEP, the treatment of cancer was once considered an "incredible utility." However, the use of certain agents such as Platinol® (cisplatin) in testicular cancer is successful in approximately 70% of cases when detected early. The number of drugs currently approved for the treatment of cancers and the increasing levels of survival of cancer patients demonstrates that although there is not a cure for cancer, there are effective treatments available. One must be cognizant of the distinction between a treatment and a cure. COX-2 inhibitor drugs such as Celebrex® (celecoxib) are approved as an effective treatment for rheumatoid arthritis, but are not cures for the disease. In this instance the claimed invention relates to recombinant adenoviral vectors which selectively replicate in particular target cells. Specific examples of such vectors which selectively replicate in tumor cells are provided. While this may or may not

necessarily be a cure for cancer, it is a treatment which Applicants believes will ultimately be useful in the treatment of the disease in human beings.

As a final note, the Applicants would suggest that there is reason to believe that this therapy would not generally be considered as "gene therapy" but rather "viral therapy." In the case of one attenuated viral vector (ONYX-015) submitted for clinical trial approval to the Recombinant Advisory Committee ("RAC),the RAC indicated that its approval was not required because this constituted viral therapy not gene therapy. (Applicants can provide copies of this correspondence if required.) There is reason to believe that the vectors of the present invention might be considered similarly since they are designed to selectively replicate in and lyse the cell subject to infection. Consequently, the Examiner's suggestion that the vectors of the present invention are "gene therapy" is open to question.

(3) Transformed Cells of Claim 34:

Claim 34 stands rejected pursuant to 35 U.S.C. 112 first paragraph for failing to provide an enabling disclosure. Applicant was unable to identify any specific comments regarding the subject matter of claim 34 in the Office Action to which to address a reply. Applicant therefore offers the following comments regarding the subject matter of this claim. The specification provides numerous examples of cells transformed with the conditionally replicating vectors of the present invention. See the data presented in Tables 2 and 5 and the process described for producing the vectors in 293 cells. Each of these is an example of a cell transformed with a selectively replicating vector of the present invention. Applicant therefore believes that this ground of rejection is improper and therefore respectfully requests that this rejection be withdrawn.

(4) Selective Promoter Claims 35-36:

Claims 35 and 36 stand rejected pursuant to 35 U.S.C. 112 first paragraph. Applicant is unclear of the Examiner's position in regard to the claimed subject matter. In the Office Action, the Examiner states:

> The *in vitro* examples and results on pages 13-16, shows that the Applicant was successful in producing the TGF-beta pathway responsive promoter by incorporating sequences from plasminogen activator inhibitor-1 (PAI-1 promoter) or binding sites for Smad4/DPC4 (SRE-promoter) upstream of the SV-40 TATA box. The results demonstrate that the PAI and SRE promoters are active only in cells with a functional TGF-beta signal transduction, as indicated by the luciferase expression. Applicant was also successful in showing the results obtained when PAI promoter operably linked to a repressor of viral replication, E2F-Rb, selectively repressed E2 promoter in cells with intact TGF-beta pathway. In addition, application indicated that the response elements p53 CON and Rb promoters were active in cells functional p53 and that the activity of the p53 responsive promoter increased in a dose dependent manner with increasing p53 activity. (Office Action at page 4).

and,

> The *in vitro* examples and results on pages 13-16, shows that Applicant was successful in producing the TGF-beta pathway responsive promoters by incorporating sequences from plasminogen activator inhibitor-1 (PAI-1 promoter) or binding sites for Smad4/DPC4 (SRE promoter) upstream of SV-40 TATA box. The results demonstrate that the PAI and SRE promoters are active only in cells with a functional TGF-beta signal transduction, as indicated by luciferase expression. Applicant was also successful in showing the results obtained when PAI promoter operably linked to a repressor of viral replication E2F-Rb, selectively repressed E2 promoter in cells with intact TGF-beta pathway. In addition, Applicant indicated that the response elements p53CON and RGC-promoters were active in cells with functional p53, and the activity of the p53 responsive promoter increased in a dose-dependent manner with increasing p53 activity. (Office Action at Page 4-5)

However, at page 6 of the Office Action, the Examiner states:

> The specification fails to provide an enabling disclosure as no teachings are present which would guide the skilled artisan with any degree of specifics in the construction of the pathway responsive promoters mentioned on pages 12-15. It should be noted that the isolation of promoter regions is an unpredictable field requiring extensive experimental practice to identify particular transcription regulatory regions.

The specification at pages 12-15 specifically relates to the p53 and TGF-beta responsive promoters which are the subject matter of claims 35-36. The Applicants have provided specific teaching regarding the construction of these promoters in Examples 2-4 including specifics of the DNA sequences used to generate the promoters. The data presented at pages 12-15 of the specification provides demonstration of the selective nature of the promoters. In view of the Examiner's comments at page 4 and 4-5 of the Office Action and the specific teachings of the Examples, Applicants believe that the subject matter of claims 35-36 is enabled by the specification and respectfully requests that the rejection of claims 35-36 pursuant to 35 U.S.C. 112, first paragraph be withdrawn.

SUMMARY

Based on the foregoing, Applicant believes a well-grounded scientific basis for the utility of the claimed vectors, pharmaceutical formulations comprising these vectors and the practice of the claimed methods has been provided. The alleged utility of a composition set forth by the Applicant should be considered as sufficient in the absence of distinct evidence provided by the Examiner to the contrary. Other than the general observations on the state of the art, the Examiner has provided no distinct references on-point that address the function of the claimed invention. In contrast, the Applicant has provided numerous scientific and patent references to support the scientific basis and utility of the claimed invention. Although the present invention

relates to a complex art and evolving technology, this is an insufficient basis on which to reject the claimed invention absent some specific scientifically based reasons to question the utility of the claimed compounds. Applicant therefore believes that he has satisfied the burden of demonstrating that the subject matter of the claims is enabled in accordance with 35 U.S.C. 112, first paragraph.

Applicant believes that all grounds of rejection set forth in the Office Action of January 21, 2000 have been traversed for the foregoing reasons of fact and law. Applicant therefore respectfully requests that all grounds of rejection of the pending claims be withdrawn and this case passed to issuance without delay.

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Dated: July 21, 2000

Respectfully submitted,

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